CANCER: WHAT WE KNOW TODAY

Symposium

THE EIGHTH A. WALTER SUITER LECTURE

under the auspices of the Committee on Public Health of
The New York Academy of Medicine
with the cooperation of the New York City Cancer Committee

I. The Changing Incidence of Cancer Throughout Life
HAROLD F. DORN, Ph.D.—Chief, Offices of Biometry, National Institutes of Health, Bethesda, Maryland

II. Multiple Views on the Causation of Cancer
HAROLD L. STEWART—Chief, Pathologic Anatomy Branch, Clinical Center, National Institutes of Health, Bethesda, Maryland

III. The Natural History and Early Diagnosis of Cancer*
LAUREN V. ACKERMAN—Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Missouri

IV. Modern Therapeutic Measures in Cancer and Their Effectiveness

A. Surgery
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B. Radiology
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* Manuscript not submitted.

THE CHANGING INCIDENCE OF CANCER THROUGHOUT LIFE*

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CANCER may develop at any age during the life span. Although generally considered to be a disease of late adult life and old age, it is the leading cause of death from disease among persons between five and twenty years of age. During 1951, 18 per cent of the deaths from disease at these ages were attributed to cancer. Accidents, of course, are the leading cause of death during this age period.

Each year about 330 new cases of cancer are diagnosed among every 100,000 white persons. Due principally to a lower susceptibility to cancer of the skin, the incidence of cancer is nearly 20 per cent less among non-white than among white persons, the rate being approximately 270 per 100,000 per year. Using these incidence rates, which are based upon morbidity surveys conducted by the National Cancer Institute, it is estimated that 530,000 new cases of cancer were diagnosed in the United States during 1953. Preliminary statistics from the National Office of Vital Statistics reveal that 223,000 deaths were attributed to cancer in 1953.

While these statistics convey a general impression of the magnitude of cancer as a medical problem, they do not even suggest the diversity of ways in which this disease manifests itself. For cancer appears to be a disease or group of diseases of multiple etiology and manifold forms. What do we know concerning the variation in the incidence of cancer throughout the life span and what does this variation suggest concerning the etiology of cancer?

Although cancer may occur at any age throughout the life span, the incidence rate (number of newly diagnosed cases per 100,000 population per year) varies widely among persons of different ages (Fig. 1). The lowest incidence is found among children from five to fifteen

* Presented at the Stated Meeting of The New York Academy of Medicine, November 4, 1954, as part of the Eighth A. Walter Suiter Lecture program. This meeting was arranged by the Committee on Public Health with the cooperation of the New York City Cancer Committee, as a Symposium on "Cancer — What We Know Today".

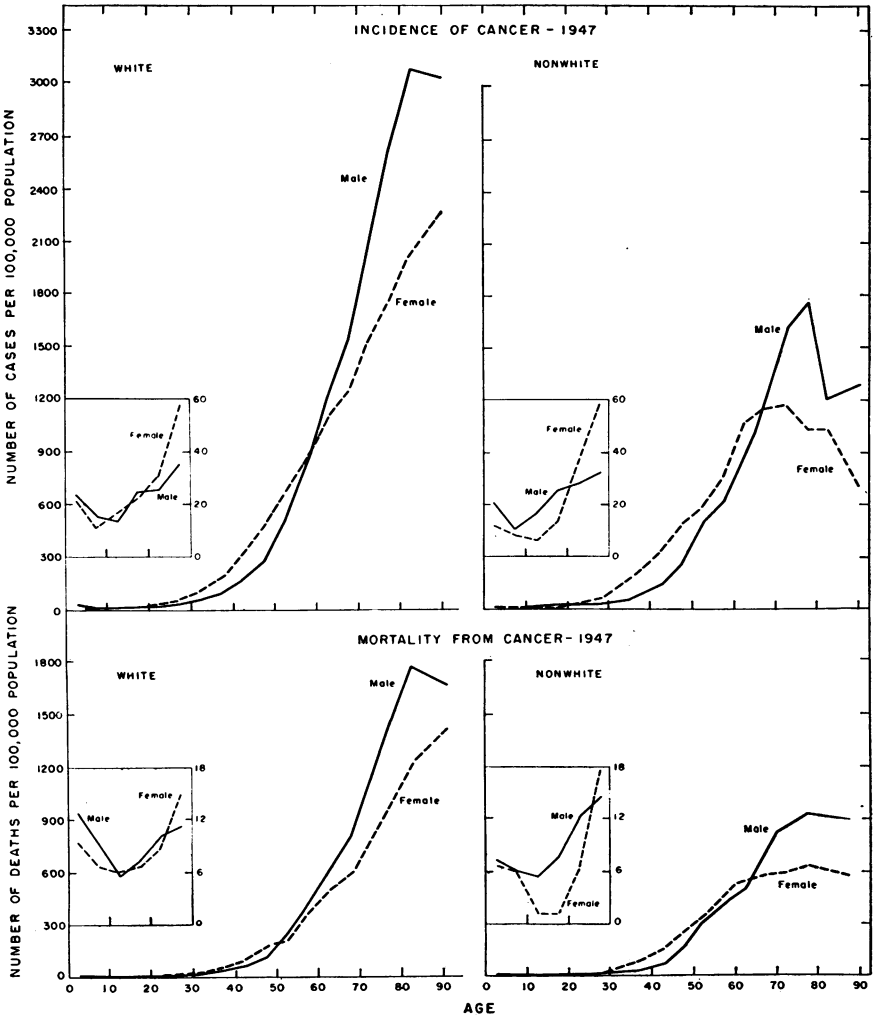

Figure 1—Incidence and mortality rates per 100,000 population from cancer by age, sex and color, selected urban areas, United States, 1947-48.

years of age when the annual number of newly diagnosed cases is about 13 per 100,000. After age fifteen the chance of developing cancer increases rapidly. By age ninety, the increase is two hundredfold.

At, and shortly after birth—0 to 4 years of age—the incidence rate of cancer is 65 per cent greater than that toward the end of the first decade of life. The decline in the incidence rate between birth and puberty, as well as the change in the parts of the body where cancer is most likely to develop, suggest that different etiological agents begin to operate after puberty.

The organs and tissues of the body that are most susceptible to cancer during infancy and early childhood differ strikingly from those that are most susceptible during the final years of life. During infancy and childhood—the first decade of life—90 per cent of malignant neoplasms develop in the blood or blood-forming organs, connective tissue, neural tissue or are tumors of embryonal or mixed tissues. About two-thirds of new cancers are found in hematopoietic or neural tissue alone. Next in relative importance are tumors of mesenchymal, embryonal and mixed tissues. Malignant melanoma and malignant tumors of epithelial tissue are rare during the first few years of life. In contrast, during the last third of the life span—sixty-five or more years of age—only 7 per cent of malignant neoplasms are of the histological types most common in infancy and childhood.

Around puberty (ten to fourteen years of age) the types of cancer are similar to those appearing during infancy and childhood. At this period of life, malignant neoplasms are more restricted as to site than at any other age period; 80 per cent occur in four tissues—brain, bone, hematopoietic and lymphatic.

The termination of puberty is followed by a pronounced change both in the histological type and primary site of cancer. From infancy until puberty the incidence rate declines, and the vast majority of malignant tumors develop in a relatively few organs and tissues. Whatever the etiological agents during this period of life, their effect steadily decreases and by the end of puberty has become comparatively negligible.

Immediately following puberty the incidence rate for all forms of malignant tumors begins to increase rapidly, so that by age twenty it again is as high as it was in early infancy. From then until the last years of the life span the incidence of cancer steadily increases.

Not only does the incidence of cancer become greater, but the relative frequencies of both the histological types and primary sites also change markedly. The achievement of sexual maturity is followed by an increase in the incidence of malignant tumors arising in embryonal and mixed tissues—in the ovary in females and in the testis in males. These types quickly are overshadowed by carcinoma, which becomes the dominant type of malignant neoplasm during adult life and extreme old age (Fig. 2). The incidence rates of sarcoma and melanoma also continue to rise throughout the life span, but the increase in the

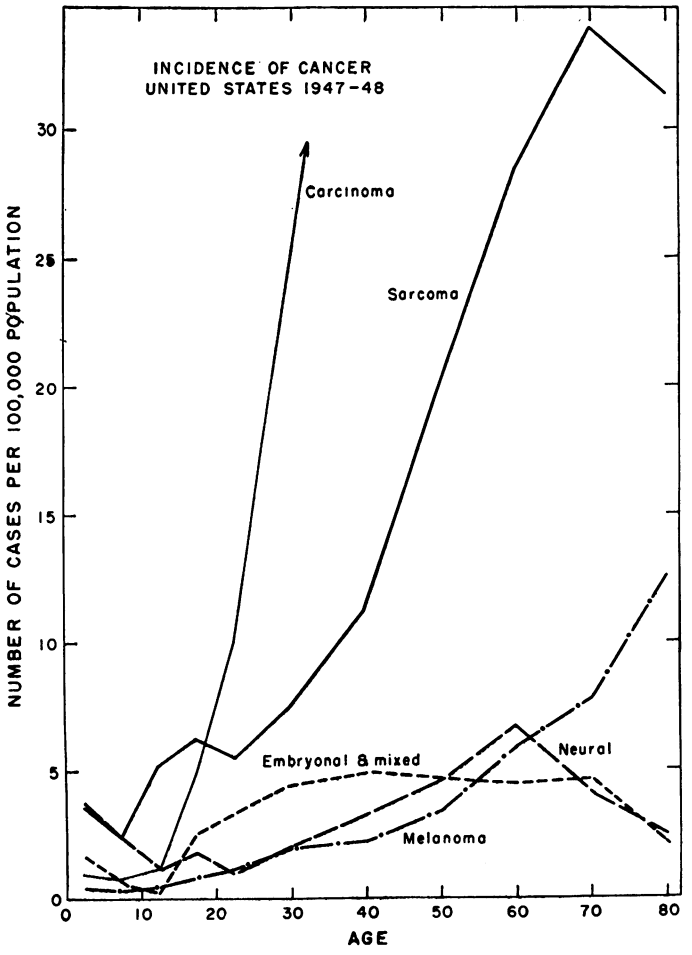

Figure 2—Incidence rates per 100,000 population from cancer by age and histological type, selected urban areas, United States, 1947-48.

incidence of carcinoma is so much greater that their relative frequency decreases.

During adolescence and early adult life cancer appears in parts of the body where previously it has been rare or nonexistent—tongue, esophagus, small intestine, biliary passages, stomach, larynx, uterus, vulva and vagina. The prostate is the last organ to become a frequent site of cancer. Clinically active malignant tumors of the prostate are very rare prior to age forty. After this age, the incidence of prostatic cancer begins to increase fairly rapidly, so that among males aged sixty-five years and over about one out of every six malignant tumors originates in this gland.

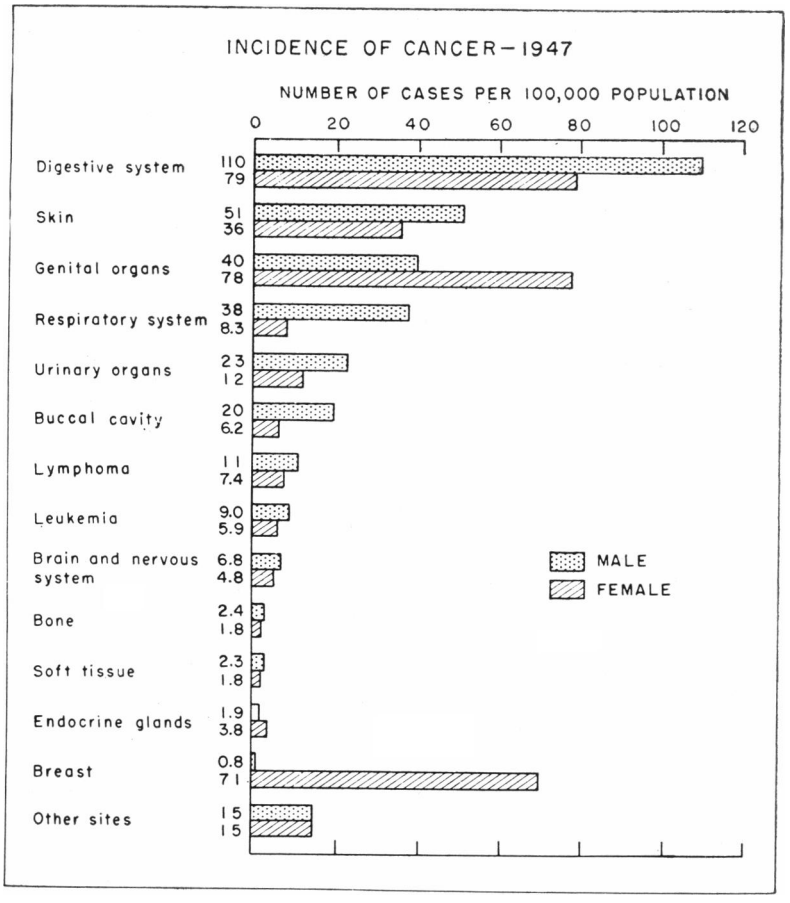

Figure 3—Incidence rates per 100,000 population from cancer by sex for broad groups of primary sites, selected urban areas, United States, 1947-48 (age-adjusted rates based on total U. S. population, 1950).

In spite of the fact that cancer may develop in any organ or tissue during adult life, the majority of new growths originate in a few sites (Fig. 3). More than one-half of the cancers among adult females are found in the breast, uterus, and skin. Approximately the same proportion of malignant tumors among males originate in the digestive system, lung, and skin.

The sharp change in the incidence of cancer following puberty brings into focus a fact that previously had not been obvious—the difference in frequency with which cancer attacks the various organs and tissues in males and females. Males start life with a slightly greater risk of developing cancer. The sex differential is not particularly striking,

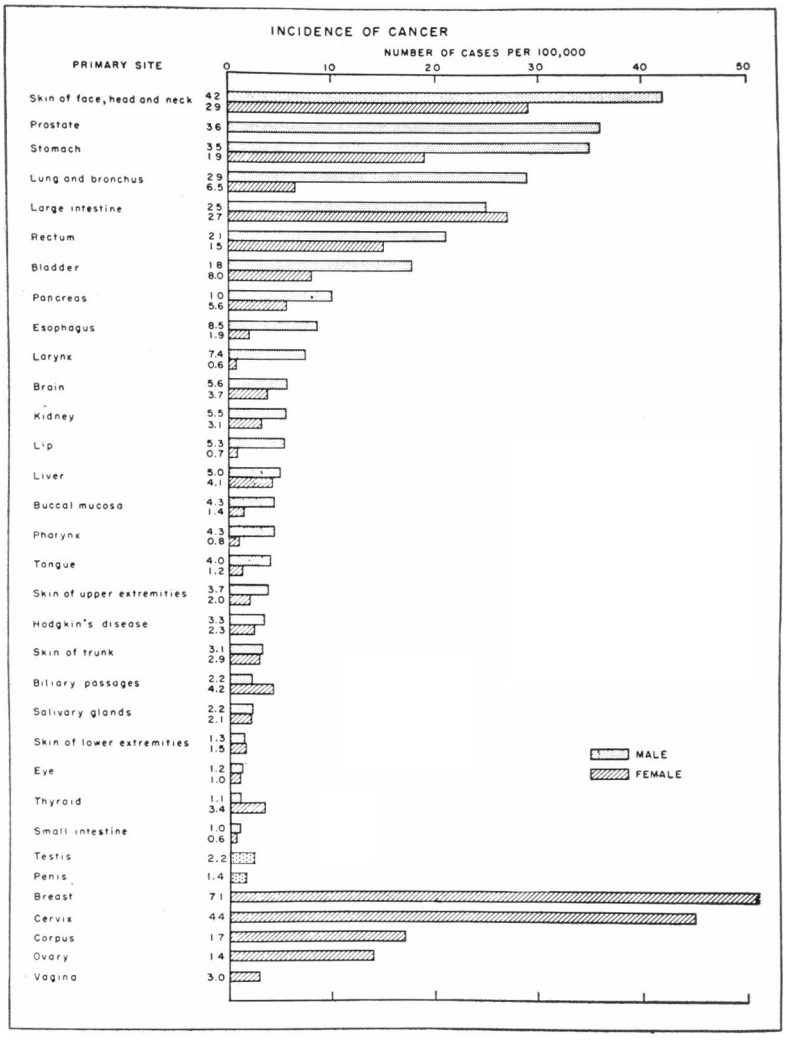

Figure 4—Cancer of specific primary sites: Incidence rates per 100,000 population by sex, selected urban areas, United States, 1947-48 (age-adjusted rates based on total U. S. population, 1950).

and the relative frequency with which cancer develops at various anatomical sites is essentially the same for each sex.

Following puberty, the incidence rate increases more rapidly among females, so that by age twenty the rate is approximately the same for both sexes. Fifteen years later—by age thirty-five—the annual number of new cases of cancer per 100,000 is twice as great for females as for males. After the usual ages of menopause, the rate of increase in the

incidence of cancer among females slackens. Between sixty and seventy years of age, the incidence rate again is greater for men than for women, a relative standing that is maintained the remainder of the life span.

This sex variation in incidence is the net effect of the widely varying susceptibility of different organs and tissues to cancer. The most impressive difference in susceptibility is for the reproductive system—the breast and genital organs. Nearly one-half—45 per cent—of all new malignant growths among females originate in the breast or genital organs. In contrast, only one in eight or twelve out of every 100 males who develop a malignant neoplasm will have cancer of these sites. The greatest difference is for the breast. Cancer of this site is very rare among males but accounts for one out of every five new malignant growths among females.

All of the other common forms of cancer occur more frequently among males than among females (Fig. 4). Two rather rare forms, cancer of the biliary passages and cancer of the thyroid, are more common among females, while cancer of the large intestine, salivary glands and skin of the lower extremities is equally likely to develop in each sex. Excluding cancer of the breast and genital organs, the incidence rate per 100,000 becomes 290 for males and 181 for females, a relative difference in risk of 60 per cent. This suggests that males are more susceptible to cancer or that they are more exposed to environmental carcinogenic agents.

The incidence rate for cancer of the female reproductive system is 3.7 times that for the male reproductive system. But this ratio varies widely throughout the life span, a fact which suggests the existence of different etiological agents.

Prior to puberty the incidence of cancer of the reproductive system is about equal for each sex (Fig. 5). After puberty the picture changes rapidly. By age thirty the incidence rate for cancer of the reproductive system among females exceeds the incidence rate for all forms of cancer among males. This relative standing continues for about twenty years. Not until age fifty is reached does the incidence of all forms of cancer among males exceed the incidence of cancer of the reproductive system among females.

Cancer of the male reproductive system remains relatively unimportant until about age fifty. For the age group forty-five to forty-nine years, the incidence rate is 7.7 per 100,000 population per year. During

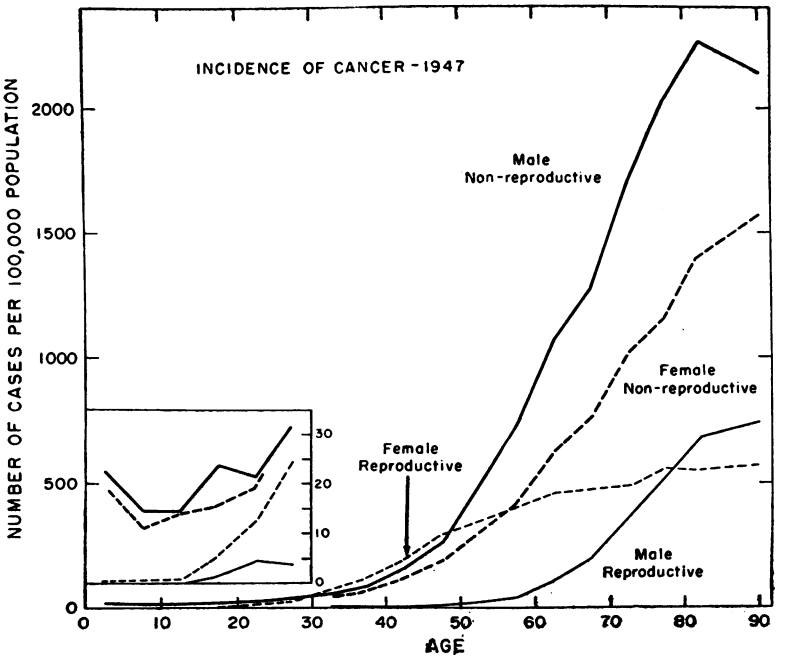

Figure 5—Cancer of reproductive and non-reproductive organs: Incidence rates per 100,000 population by age and sex, selected urban areas, United States, 1947-48.

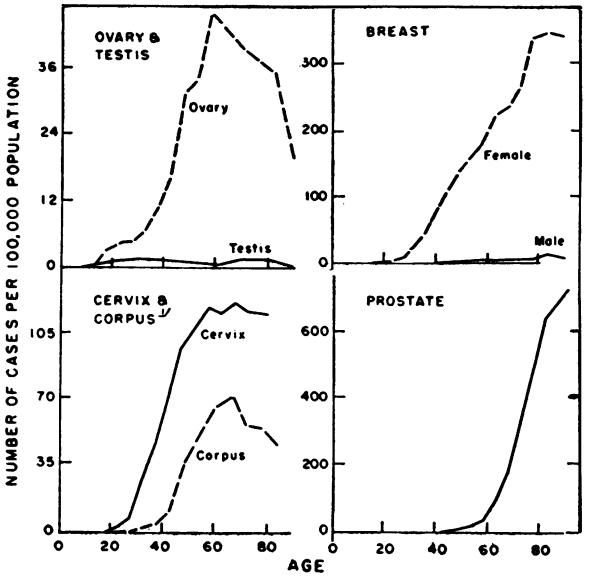

Figure 6—Cancer of specific reproductive organs: Incidence rates per 100,000 population by age and sex, selected urban areas, United States, 1947-48.

the next forty years the rate increases one hundredfold, reaching a level of 779 for the age group eighty-five years and over. Practically all of this sharp rise results from an increase in the incidence rate of cancer of the prostate.

The separate reproductive organs have distinctive incidence curves (Fig. 6). The curves for cancer of the ovary, cervix uteri, corpus uteri and prostate rise steeply from an initial low point to a maximum within a period of from 20 to 30 years. The location of this period within the life span, however, differs for each form of cancer, a fact which suggests that the occurrence of these cancers is related to physiological changes in the functioning of the organs.

The incidence rate of cancer of the breast, for females and males alike, continuously increases throughout the entire life span even though the absolute level finally reached is nearly thirty times greater for females than for males. The testis is the only reproductive organ for which the incidence rate does not increase with advancing age. Prior to puberty malignant tumors of the testis are very rare. Following puberty, the rate rises to a level of between 3 and 4 per 100,000 by age twenty-five, a level which is maintained throughout the remainder of the life span.

The picture presented by cancer of the non-reproductive organs and tissues is in sharp contrast to that for cancer of the reproductive system. Although the neoplasms of the non-reproductive system include a diversity of tumors, probably of separate etiology, all but a few have one thing in common—their incidence is greater among males than among females.

The excess for males is not great during the first three decades of life, but after age thirty it rapidly becomes larger. By age forty, the incidence rate for males is about 30 per cent greater than that for females; after another fifteen years—age fifty-five—the differential has reached 75 per cent and continues at that level throughout the remainder of the life span.

There are many lessons to be learned from a careful study of the incidence of cancer in different population groups. These are applicable both to detection and case finding for purposes of therapy and to the study of etiology. The more completely we understand the natural history of cancer as a disease of human populations, the better prepared will we be to develop methods for its control.

MULTIPLE VIEWS ON THE CAUSATION OF CANCER*

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I CERTAINLY share with the late Dr. Suiter the feeling that if we knew the causes of most of the cancers that we see today we would be in a much better position to prevent them. Certainly preventive medicine is obviously one of the chief methods by which we may hope that cancer may be controlled.

Hueper has stated that we know the cause of only 1 per cent of the cancers that we see in everyday practice. We know the causes of some groups of cancer. We know some carcinogenic agents that people are exposed to. Taking the individual case of cancer, say of the stomach, of the pancreas, of the bowel, of the lung, or of the skin, we know the cause of perhaps less than one per cent of these cancers. So I would like to mention some of the carcinogenic agents that act on human beings, to discuss how these agents have been discovered and to say something about their mode of action.

In a recent monograph dealing with environmental cancer and industrial cancer, Hueper[1] gives a list of substances which may cause cancer in man. Most of you are familiar with many of these substances and agents as they have been known for years. Deposits of inorganic arsenic in the skin may induce skin cancers of the trunk. The problem of skin cancers due to tars, shale oil, petroleum products is an old story dating back to the days of Percival Pott, who first described cancer of the scrotum in chimney sweeps. People working in the dye industry, exposed to aromatic amines may develop cancer of the bladder. This was noted by factory physicians in Europe many years ago, and the disease has been reproduced experimentally in the dog by Hueper and in other animals by workers in England. Solar radiation of course is a well

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known cause of skin cancers. Skin cancers from this cause are seen more frequently in sailors, ranchers and farmers than they are in people who are not so heavily exposed to sunlight. In the survey of the morbidity of cancer in different cities of the United States, the incidence rate of skin cancer was higher in the Southern than in the Northern cities. In Atlanta the incidence rate was 157 as compared to twenty-four in Detroit. Cancer may be caused by radiation or exposure to radioactive chemicals. As is well known the early radiologists frequently developed cancer of the skin from excessive exposure of their hands in the beam of the x-ray. The lung cancers that developed in the Schneeberg miners, who mined radioactive ores have been attributed to the effects of radioactivity. It is well known that the late Harrison Martland observed that workers who used radium-containing paint and who moistened their paint brushes with their lips, develop bone tumors from the radium deposited in the bones. Leukemia is seen more frequently in radiologists than in physicians who are not exposed so heavily to radiation. I believe it was Dr. Fred Stewart of this city who described some of the early cases of primary sarcoma induced in the normal soft tissues which were included in the field of radiation for malignant tumors. There have also been reports, some of them not well documented, of a higher incidence of lung cancer in workers in certain industries such as workers with asbestos, with the chromates, and those in the nickel industry. Benzene deposits in bone marrow may initiate leukemia. In the manufacture of isopropyl alcohol from propylene gas, there appears to be a higher than expected incidence of cancer of the lung and of the nasal sinuses. Exactly what substance these latter cancers are due to no one knows. Thermic trauma, of course, is a well known cause of cancer of the skin. Third degree burns, not infrequently, eventuate years later in squamous cell carcinoma. The problem of bladder cancer in Egypt has been discussed at great length and it is believed by many people in Egypt that it is due to the marked infestation with schistosoma, that occurs in that country, particularly among the farmers. Schistosoma haematobium, which is the common organism in Egypt, is also an infective agent in West Africa and South Africa. I am told that the high incidence of bladder cancer seen in Egypt does not occur in these latter locations.

Why is the cause of cancer so difficult to discover? One reason is that people are exposed years before the cancer develops. The age

distribution of cancer of the bladder due to aromatic amines illustrates that point very well. For example, individuals working with this dye from the ages of fourteen to twenty-nine years developed their bladder cancers between the ages of thirty to thirty-nine, forty to forty-nine and fifty to fifty-nine. However, if they were thirty to forty years of age when they began to work their cancers appeared later in life, chiefly between the ages of fifty to fifty-nine, and sixty to sixty-nine years. When they entered on the job still later, at ages forty-one and forty-two years, the latent period shifted still further and their cancers appeared chiefly at ages sixty to sixty-nine and seventy to seventy-nine. It is difficult, in the case of a man dying of cancer at seventy-nine years of age, to go back into his history to discover to what possible carcinogens he had been exposed in his earlier life. He may have had a short exposure to one of the dyes like beta-naphthylamine in a job that he may have had for only a relatively few years.

Some substances have been developed which were designed to be either medicinal agents or insecticides. People might have been exposed to these compounds on a wide scale had not these substances, as the result of laboratory investigation, been shown to be carinogenic. I wish to mention two of those listed in the paper by Hueper;[1] styryl 430, developed as a trypanocidal agent was shown to be a carcinogen; and 2-acetyl amino fluorene, developed as an insecticide, is one of the most potent carcinogens we have for animal work. Cancer may be induced with 2-acetyl amino fluorene in at least four species of animals and these cancers may occur in a great variety of tissues and organs,—the subcutaneous tissue, the bladder, liver, brain, thyroid gland, breast, kidney and so forth. It is fortunate indeed that these substances were identified as carcinogens before being marketed.

I would also like to mention a few other substances, to which man is exposed and that have proved to be carcinogenic for animals. It is not known whether they are carcinogenic for man or not. One of the common ones is estrogen, a highly potent carcinogen for the rat, rabbit and guinea pig, producing a variety of tumors in these animals. We do not know for certain whether or not estrogens are carcinogenic for human beings. Three other substances I might mention that are carcinogenic for animals are carbon tetrachloride, chloroform and DDT. All produce tumors in the liver either in the rabbit or mouse. There are certain dyes that might be mentioned—Light Green SF, Brilliant Green

FCF, which have been used as textile dyes, food and cosmetic dyes, and which have produced subcutaneous sarcomas in the rat. As the result of the work of Oppenheimer and Stout of this city, cellophane is well known as a carcinogen. This and other plastic substances are carcinogenic for the rat, producing subcutaneous sarcomas. I understand there are fourteen of these plastic substances now known to be carcinogenic. Other substances that also fall into this category are: thiourea, which produces liver cancer in the rat; Dulcin, an artificial sweetening agent, produces cancer in the rat, and methylated naphthalene, which is used as a solvent vehicle for insecticides, is carcinogenic for the skin of mice. Many of the insecticides which use methylated naphthalene as a vehicle are used in the household, and the housewife is, therefore, particularly exposed.

There are some curious cancers. They do not contribute much to the overall picture of cancer but there are some neoplasms that seem to be related to regional habits and customs. The Khaini and betel nut cancer is common in India where there is a great deal of oral cancer and where the habit of chewing the betel nut with the betel leaf lime and tobacco is widespread. There has been no really serious work done on this problem and yet the textbooks all say that these are cancer-inducing agents. On the other hand, in Indonesia, where betel nut is chewed just as much as in India, there is very little oral cancer. I think it is time to set up a serious study on these habits to see if they really are the cause of the large amount of oral cancer that is seen in India.

There are also a number of cancers that are due to thermal injuries,—burns. The Chutta cancer occurs in India where the people have the habit of smoking a cigar with the lighted end inside the mouth. There is also the Kang cancer, found in the people of Northern China, who sleep on a "kang" which is a perforated mat. They place hot bricks beneath the bed and during their sleep they develop burns and later cancer. People in the Himalayas carry baskets containing heated coals and get burns of the skin from which cancer arises.

The question of heredity must also be considered. So far as we know at present, heredity accounts for very little cancer in the human race. In the laboratory we have pure strains of mice that have been bred brother-sister for more than twenty generations. These particular animals may show a high incidence of cancer in one or another site: a high incidence of leukemia in one strain, a high incidence of lung can-

cer in another strain. But the human race is so heterogeneous, genetically speaking, that there is no opportunity for anything like that to develop. There are four cancers in man that have a hereditary background, retinoblastoma, neurofibrosis, intestinal polyposis, xeroderma pigmentosum. In the case of xeroderma pigmentosum, individuals with this condition are born not with cancer or with the hereditary tendency for cancer but with a hereditary tendency for sensitivity to ultraviolet light and being sensitive to sunlight, they develop a high incidence of skin cancer upon exposure. There have been some studies on twins, in certain families, where it was thought there was a high incidence of cancer of specific types and organs, but this has really not been confirmed statistically.

Then there are some cancers that appear to arise on the basis of demographic conditions. Among these are the oral-pharyngeal cancer of Scandinavian women living in the northern part of that region. During the long winter they live on salt fish and reindeer meat with very few vegetables. They develop vitamin and iron deficiencies. The iron deficiency becomes particularly marked in the women because of loss of iron in menstrual blood. They develop the Plummer-Vinson syndrome, oral lesions, and many eventually develop cancer.

Liver cancer is an example of a cancer that is associated with undernutrition. Liver cancer occurs in a broad belt that sweeps through Africa, Indonesia, China, Japan and the Philippines. Its occurrence is associated with lack of protein, lack of vitamins, and cirrhosis of the liver.

Penile cancer is one cancer that in all probability could be prevented if all males were circumcised at an early age. There is almost no penile cancer in Jews. It is not common in Moslems who are circumcised later in life than Jews. This type of cancer occurs quite frequently in the uncircumcised in some parts of the world and it is one type of cancer that might be prevented by simple circumcision in the first few days of life.

Steiner[2] has made an interesting study of different races in the autopsy material of the Los Angeles County Hospital and found definite differences in the occurrence of cancer in Mexicans, Negroids, Japanese and Filipinos as compared with white North Americans. He noted that Mexican women have a high incidence of cancer of the lung and larynx as compared with American women.

Although we may not know the causes of certain cancers we know certain selective factors about people who develop these cancers. Two of these are cancer of the breast and cancer of the uterus, about which I will speak only briefly. The breast cancer patient is usually a woman in a relatively high economic status. White American women develop this disease more frequently than Negro women. The incidence is low in Japanese women, being only about 1/6 to 1/8 what it is in American white women. Whether or not that may be because the Japanese woman has a small breast is difficult to say. It occurs more frequently in single women than in women who are married. In married women it is more frequent in those who marry late in life and exhibit reduced fertility.

By contrast cancer of the uterine cervix shows almost a reverse type of selective factors. The women who develop cancer of the cervix are of a relatively low economic status. That generalization does not apply to individual cases, but on the whole more of the patients with cervical cancer are in a lower social status than are those women with breast cancer. In the United States cancer of the cervix is more frequent in Negro women than in white women, more frequent in married than in unmarried women and is more frequent in women who marry young and have many children. Circumcision of the mate possibly plays a part because cancer of the cervix is much less frequent in Jewish women than in American or European non-Jewish women. Cervical cancer is less frequent in Moslem women than it is in Hindu women. These differences are striking but they still do not elucidate the real cause.

Finally, I wish to discuss briefly the methods by which carcinogenic agents act to produce cancer. Carcinogens may act directly,—excessive exposure to ultraviolet light on the skin is an example. A carcinogen may act at the site at which it is deposited, as in cancer of the bone where radium is deposited. A carcinogen may act on an organ of excretion, such as the aromatic amines in inducing cancer of the bladder. A carcinogenic effect may be mediated through a functional tissue or a functional deficiency as for example, the thyroid gland and iodine deficiency. There is a higher incidence of thyroid gland cancer in areas where there is an iodine deficiency. Carcinoma of the oral pharynx and esophagus, in women who are undernourished, as in those who suffer from malnutrition in Northern Scandinavia, is another example.

There are two other mechanisms I would like to mention briefly. We have no information on them with respect to human beings but they have been shown to be of importance in laboratory animals. When the carcinogen urethane, which induces lung cancer in mice, is given to a pregnant mouse, the offspring of that mother will develop cancer in the lung. In other words, here is one carcinogen that crosses the placental barrier and sets up the malignant process in the lung of the embryo. Another route, as shown by Shay of Philadelphia not long ago, is by way of the lactating mother. When methylcholanthrene is administered orally to lactating rats, the offspring who suckled those mothers developed acute leukemia. These two routes that ordinarily might not be thought of, should be kept in mind for they may be of help in elucidating causes of human cancer now unknown.

In closing I would like to note that the causes of the cancers about which we know most were discovered largely by the practicing physician, the dermatologist, the surgeon, the pathologist, practitioners who were seeing patients. I firmly believe that if the practicing physicians of this country were to concentrate on this particular problem and try to do a thorough piece of investigation, the number of known causes of cancer would increase rapidly. It is the general practitioner who first sees the cancer patient. He often knows the patient well. He often possesses knowledge of where and under what conditions the person has worked, and to what possible carcinogens he has been exposed. It would be well worth while if the practitioners of this country, who individually do not see too many cancers in a year's time, would devote themselves to trying to determine what might have been predisposing factors in causation of cancers in the patients they see in consultation.

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THE EFFECTIVENESS OF SURGERY IN THE MANAGEMENT OF ALIMENTARY TRACT CANCER WITH SPECIAL REFERENCE TO THE STOMACH AND COLON*

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My role in this symposial discussion is to say something of the effectiveness of surgery in the management of cancer. In a sense this is easily said in a few words: if cancer is recognized and treated while the disease is local it is curable. Moreover, there is a big disparity in accomplishment when the lymph nodes are involved, as contrasted with the promise when excision is done while the disease is still local, and the regional lymph nodes are free of cancer. I would be less than realistic if I failed to indicate that the overall accomplishment in the management of cancer is not what we would have it be. One reason for the poor present day accomplishment is that we are still largely treating symptomatic cancer. It is particularly unfortunate that the silent interval of visceral cancer is so long. However much we bemoan the circumstance that patients having visceral cancer may not come immediately when symptoms supervene, or that the doctor may fail to interpret their significance correctly, the far more important circumstance is that the silent interval in most visceral cancers is in the area of twenty months. Even early symptomatic visceral cancers are therefore of approximately two years' duration when operation is undertaken. The meaning is perfectly clear: until biological tests become available, we shall have to continue screening age populations in which the incidence of cancer mounts sharply in the hope that the presence of asymptomatic cancers can be detected.

During the depression, money in our banks earned only 1 per cent. The yield of asymptomatic cancers discovered in the Cancer Detection Centers appears to be somewhere between 2 and 3 per cent,

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when patients of fifty years or more are screened carefully with a view to uncovering silent cancers. In some parts of our country, Cancer Detection Centers are struggling for existence. Some physicians would have us believe that the few cancers found do not justify the arduous labors involved in unearthing silent cancers. Most of us count life amongst the most valuable of terrestrial assets. To have a cancer detected when the disease is local and curable is a discovery of momentous importance to the person whose cancer it is.

The prayer and silent hope on the lips of everyone who has any contact with the problem of cancer—and mind you all of us are eventually potential cancer sufferers—is that presently there will be available diagnostic biological or organ scrutiny tests which will help make less toilsome the present heavy labors of Cancer Detection Centers.

What I shall have to say here concerns cancer of the alimentary tract and I will speak primarily of two cancers with which I have been especially concerned: cancer of the stomach and cancer of the colon.

Esophagus

Apart from leukoplakia, the precursors of esophageal cancer are not known. It is predominantly a cancer of males, save for cancer of the hypopharynx. It does seem odd that obstruction of this conduit of the alimentary canal is often complete before the presence of the cancer is recognized. It is becoming increasingly evident that too many surgeons in operating for esophageal cancer have divided the esophagus too close to the cancer on the proximal side—a circumstance which accounts in large measure for the paucity of five year survivals reported from some clinics.[1] Even for a juxta-gastric-lying esophageal cancer, it would appear in order to effect the anastomosis at the level at which the azygos vein joins the superior vena cava. Reports of Sweet[2, 3] indicate the cure rate in cancer of the distal third of the esophagus following radical surgery, particularly if the lymph nodes are uninvolved, compares quite favorably with many cancers of the alimentary tract.

Stomach

Achlorhydria frequently accompanies gastric cancer. Whereas the incidence of achlorhydria in patients over fifty years of age having extragastric malignancies is essentially that of the same age group (approximately 33 per cent), in gastric cancer this figure is doubled, as

was indicated in an earlier report from this clinic.[4] Moreover, routine use of gastric aspiration, employing histamine as a stimulant, leads to the discovery of a number of achlorhydric patients harboring gastric polyps. To be certain, all patients with gastric cancer are not achlorhydric; nevertheless, of the available present day screening techniques to apply with a view to uncovering silent gastric cancers, the finding of achlorhydria on gastric aspiration is the best. In this clinic it has long been common practice to submit all patients who are found to be achlorhydric or hypochlorhydric (less than 30° free HCl after histamine) to careful roentgen examination of the stomach. The experience of this clinic suggests that 80 per cent of patients with gastric cancer are either achlorhydric or hypochlorhydric on histamine stimulation. And over the years, during which achlorhydric patients have been submitted to routine x-ray examination of the stomach, ninety-six patients were found to be sheltering gastric polyps. These patients are uniformly achlorhydric. These lesions are slow but definite precursors of gastric cancer. Of gastric polyps more than 2 cm. in diameter, 50 per cent were malignant. The overall incidence of cancer in the thirty-two patients in this group submitted to operation was 21.8 per cent.[5] The practice of this clinic has been to scrutinize these patients carefully by roentgen and gastroscopic examinations three times a year. Increase in size of the polyps is regarded as an indication for operation. Similarly, failure of the patient to cooperate in the observational scrutiny is regarded too as an indication for operation. Obviously a gastric mucosa, from which polyps germinate, does develop additional polyps occasionally in the residual gastric pouch following resection. Hence, the only complete assurance against recurrence would be total gastrectomy which, in many instances, would amount to over enthusiastic employment of a useful but aggressive form of therapy.

Of the available techniques in the recognition of gastric cancer, the roentgen rays give the most helpful aid. A pooling of information with the roentgenologist is important. Nevertheless, the method has its definite limitations; superficial spreading cancer of the stomach apparently is not readily recognized, even by expert roentgenologists. Each year I see a few patients who have complaints referable to the gastrointestinal canal in whom no lesion was observed by the roentgenologist on fluoroscopic examination or on study of x-ray films. Similarly, I occasionally see patients, too, who are being treated medically for a

gastric lesion with the sympathetic forbearance of a competent roentgenologist under the impression that the existing lesion is a benign gastric ulcer. It has been a disillusioning experience to appreciate that my chief function as a gastric consultant has been to ask the patient: has your stomach been pumped? This single question has been the means, however, of bringing many a patient with an abdominal complaint to the operating table. While in many quarters, it is still being debated whether it is worth while to pump the stomach, I find it very useful information to relay to the roentgenologist that the patient in whom he can find no lesion has pain and is achlorhydric. Moreover, the surgeon needs no approval from any one save the patient to urge operation in the presence of a demonstrable ulcerative lesion in the stomach in a patient who is found to be achlorhydric. Gastroscopic examination too may yield helpful information when the roentgenologist is unable to find a lesion in the stomach. Clinicians, including surgeons, have a responsibility in the diagnosis of gastric cancer. It is not a task to be left solely to the roentgenologist. The roentgen techniques of 1954 are not sufficient to recognize every gastric cancer. In fact the surgeon finds it necessary occasionally to urge upon the roentgenologist that a given patient may be harboring a gastric cancer. Ochsner and Blalock[6] have suggested and employed abdominal exploration in a few such cases and have succeeded in uncovering cases of symptomatic gastric cancer which were not detectable by roentgen examination. To await positive roentgen findings in such cases often is synonymous with tarrying until the lesion is inoperable.

Incision: The extrapleural sternal splitting incision gives direct access to the attic of the abdomen and is employed routinely in operations upon the stomach. It affords ready extrapleural exposure of the lower reaches of the esophagus and enables the surgeon to amputate suitable lengths of the esophagus in total gastrectomy as well as in fundic cancers. For cancers of the distal third of the esophagus, in which amputation of the esophagus should be made at the level of the azygos vein, the sternal splitting incision does not suffice.

Subtotal Versus Total Gastrectomy: Total gastrectomy somewhat more than a decade ago was accompanied by a large operative mortality in most surgical clinics of the world. All this has changed. Today, surgeons practiced in the technique of total gastrectomy can do the operation at risks which approximate those of subtotal gastrectomy. In

other words the decision to perform the procedure should be made solely on the extent of the cancer. More and more I find myself doing total gastrectomies. When the pathologist returns the opened specimen before the anastomotic procedures are commenced, it is surprising to note with what regularity cancers of the lesser curvature and the body of the stomach reach the esophageal ring. Obviously, one would not do a total gastrectomy for a pyloric cancer. However, in any gastric cancer, in order to remove the regional lymphatic drainage area completely, it is necessary to remove the gastric mesentery of the entire lesser curvature cutting it at the inferior margin of the liver; the peritoneal covering of crura of the diaphragm is removed; it is also necessary to perform splenectomy in order to remove the lymph nodes about the tail of the pancreas and in the splenic hilum. These circumstances make it mandatory to excise 85 to 90 per cent of the stomach in a patient with a pyloric cancer. The gastric omenta also are excised in toto.

It is surprising how often a cancer of the lesser curvature will encroach upon both the esophagus and the duodenum. It is obligatory therefore that the surgeon direct his notice to excising an adequate length of duodenum as well as esophagus. Excision of 3 to 4 cm. of the duodenum is standard procedure in gastric cancers of the distal third of the stomach. And in cancers which come near the esophageal ring 5 to 6 cm. or more of the esophagus are excised regularly.

All gastrojejunal anastomoses are made by the closed technique and a Roux-Y anastomosis is employed to re-establish continuity following total gastrectomy. Whereas patients do miss their gastric reservoir following total gastrectomy, it is amazing and reassuring to note how well they get on. There being no regurgitation of bile into the esophagus, erosive esophagitis with microcytic anemia, a frequent early accompaniment of end-to-side esophagojejunal anastomosis, is not observed. Within two to four years following total gastrectomy, a macrocytic pernicious-like anemia appears which responds well to treatment with vitamin B_{12}. After a brief period of adjustment in which totally gastrectomized patients must learn to eat slowly, they do very well. No substitute gastric reservoir is necessary. Such patients maintain satisfactory weight and are able to eat reasonably large meals.

The Lymph Node Dissection: No operation for cancer is complete without excision of the entire regional lymphatic drainage area. For the stomach this area is wide. Moreover, a plotting of the sites of the

residuals in "second-look" procedures undertaken in lymph node positive cases of gastric cancer has revealed an area which surgeons have failed to attack in the primary operation. These studies of my colleague, Stuart W. Arhelger,[7] suggest definitely that excision of the lymph node bearing tissues along all the structures in the pedicle of ducts and vessels going to the liver in the extreme left leaf of the gastrohepatic omentum must be done in every case of gastric cancer. In fact, the area of the portal triad has been the most frequent site of cancer residuals in "second-look" operations for gastric cancer. And since early 1954 when Arhelger's study served to point out where the residuals in gastric cancer operations were to be found, it has become regular practice in this clinic to dissect out carefully the individual structures in the hepatic pedicle including the entire length of the common bile duct as well as the cystic duct triangle. The portal vein and hepatic artery are cleared. All extraneous tissue from these structures is removed. Occasionally, the gallbladder is removed. The duodenum is rotated medially to permit removal of the lymph nodes along the terminal common bile duct and strangely enough, in approximately 40 per cent of instances, microscopic cancer is found in the primary operation in this portion of the dissection. Already, "second-look" procedures in lymph node positive cases of gastric cancer are beginning to demonstrate that this added component of the initial procedure is rewarded by a greater number of patients free from residuals at secondary operations. In fact, it becomes quite obvious that all surgeons have been doing an incomplete operation for gastric cancer.

Removal of the lymph nodes along the celiac and the hepatic arteries up to the origin of the gastroduodenal artery has been regular practice in this clinic for more than five years; and so, similarly too with removal of the lymph nodes along the superior border of the pancreas. In patients exhibiting any attachment of the cancer to the pancreas or in patients in whom the lymph nodes along the superior border of the pancreas are grossly involved, the pancreas beyond such sites is removed as a standard part of the primary operation for gastric cancer—a practice to which Allison and Borrie[8] also give strong approval. In all dissections following removal of the spleen which comes away with the stomach, the entire body and tail of the pancreas are mobilized and freed from the transverse mesocolon. When the pancreas is swung sharply to the right, the ease of making a thorough parapancreatic lymph

node dissection is augmented. Removal of the splenic artery too, facilitates dissection of the lymph node bearing tissue along the superior border of the pancreas. Splenic vein excision, however, usually demands amputation of the pancreas.

Results: The overall five year survival rate for all cases of gastric cancer seen in our clinic over the past fourteen year period (1936-1949 inclusive) is 10.3 per cent. For the six year period from 1944 through 1949, this figure is 12.4 per cent. During this fourteen year period, there have been 109 patients who survived five years or more following gastrectomy for malignancy; 104 had carcinoma; three had lymphosarcomas; and two had leiomyosarcoma. The hospital mortality for gastric resection including total gastrectomy has been 8 per cent. The five year survival rate in lymph node positive cases of gastric cancer surviving operation during this fourteen year period has been 20.7 per cent. For the lymph node negative cases, this same figure is 57.3 per cent. Of the twenty patients over the last two year interval of this study (1948-1949 inclusive) surviving gastric resection who were found at operation to be lymph node negative, fourteen or 70 per cent were alive five years later. For the lymph node positive cases surviving gastric resection during the same interval there were forty-four patients; of these only nine or 18.1 per cent survived five years.[9]

Our current program of total gastrectomy for most gastric cancers, save pyloric lesions, with the extended lymph node dissection, described herein, is demonstrating that an increasing number of patients with symptomatic gastric cancer coming to operation are lymph node positive. Of the last twenty-three patients undergoing the type of lymph node dissection described herein 87 per cent were found to have microscopic deposits in the regional lymph nodes at the primary operation—a circumstance which suggests that metastases to the lymph nodes occur with greater regularity in symptomatic gastric cancer than in symptomatic cancer of the colon. This occurrence is susceptible of at least two explanations: that cancer of the stomach is more aggressive than colic cancer; that cancer of the stomach manifests itself with a longer latent or silent interval. This observed frequency of metastatic deposits in the lymph nodes in patients with gastric cancer suggests too that, systematic complete and painstaking dissections and thorough histological examination of the excised tissues are removing patients from the lymph node negative category and placing them in the lymph

node positive group. Lymph node bearing tissues in the various areas dissected are numbered and identified as to site. More than thirty such excised specimens are distinguished regularly by label in each primary operation. Each bit of tissue excised has a gross and microscopic diagnosis with reference to the presence of cancer. The enormity of this labor is apparent. The cooperative effort of Dr. Paul Lober, pathologist to the University Hospitals, has given added meaning to these "second-look" studies which have been under way in this clinic. Moreover, it is apparent that the "second-look" project is serving as a means of teaching the surgeon helpful lessons with reference to the extent of the surgery necessary.

The Colon

Inoperable lesions of the colon are far less frequent than in the stomach. Unfortunately, a study of the five year survivors following colectomy for colic cancer in this clinic has not yet been completed. The disparity in accomplishment between lymph node positive and lymph node negative cases, so common to all cancers, was noted by Colcock[10] and the Lahey Clinic. In reporting upon 103 cases, Colcock found 64.3 per cent of the lymph node negative cases survived partial colectomy for five years; in the lymph node positive group this figure was 15 per cent.

Total or Near-Total Colectomy: Experience with total or near total colectomy in this clinic over a period of nine years,[11] during which time this procedure has become standard practice for cancer of the colon beyond the hepatic flexure, has taught that this extension of colectomy has resulted in uncovering polyps in 38 per cent of instances in an area which otherwise would not have been removed by the more conventional segmental or hemicolectomy. Moreover, an unsuspected cancer was found in another area of excised colon in 7 per cent of the instances; additionally in 11.6 per cent of the cases an operation had been done previously for colic cancer within a few months to a few years previously. In other words in 18.6 per cent of the cases a simultaneous occult or a successive colic cancer was found. These findings support the thesis that total or near-total colectomy is a justifiable procedure. There have been four hospital deaths (5 per cent mortality) in the eighty consecutive colectomies of this type which have been done since the beginning of the study in 1946.[12] No patient who retained

his ileocecal sphincter has diarrhea. In fact, unless 30 cm. or more of ileum is removed, sacrifice of the colon, with anastomosis of the ileum to the iliac colon below the sacral promontory or to the rectum, is not ordinarily accompanied by persistent diarrhea. This circumstance suggests that total or near-total colectomy too is justifiable in cancer of the ascending colon and cecum if too much ileum need not be sacrificed to remove completely the potential lymphatic drainage area. This more extended colectomy for cancer of the colon should result in salvaging additional lives from cancer. Moreover, it will make reoperation unnecessary in a rather large number of instances. With the aid of my colleague, William C. Bernstein, proctologist to the University Hospitals, complete colectomy has been applied to the problem of colic polyps and cancer in a few instances in which there were additional polyps in the rectum as well. The lesions in the rectum have been kept in check by fulguration and these patients have not developed rectal cancer. It is obvious that barium enema studies are unnecessary following this type of colectomy; a periodic proctoscopic examination suffices.

Closed colic anastomoses are made routinely in this clinic. The best preoperative preparation before operation is the administration of enemas to cleanse the bowel. Intestinal antibiotic agents are unnecessary.

The Lymph Node Dissection: Complete colectomy obviously permits wide excision of the lymphatic drainage area of the colon. Moreover, removal of the para-aortic lymph nodes in all lesions of the left colon has become standard practice in the primary operation in this clinic; in lesions of the sigmoid and of the iliac colon lying below the sacral promontory, removal of the lymphatic bearing tissue along the left external and internal iliac vessels also is in order. In lesions of the right half of the colon, a para-vena caval removal of the lymphatic bearing tissue area is a regular component of the primary operation, and in cecal lesions the dissection additionally includes stripping of the right external and internal iliac vessels of their lymphatic-bearing tissues. The mesentery of the bowel is clipped at its root insuring maximal removal of lymph node bearing tissue. The greater omentum is detached at the greater curvature of the stomach; the inferior mesenteric artery is interrupted at its origin from the aorta; the mid and right colic vessels are divided at their origins from the superior mesenteric artery and vein.

The "Second-Look" Procedure: Whereas re-entry of the abdomen

TABLE I—REOPERATIONS ON 33 PATIENTS FOR CANCER OF THE COLON

No Cancer Found at Second Look, 17 Patients

Status	*Number of Patients*	*Length of follow-up after second look (in months)*
Living and well	15	Average 29. Range 5-58
Living with residual cancer	0	—
Dead of cancer	0	—
Dead (of cause other than cancer)	2	34, 34
Operative deaths	0	—

Cancer Found at Second Look, 16 Patients

Status	*Number of Patients*	*Length of follow-up after second look (in months)*
Living and well; last look negative	5*	56, 29, 6, 63, 52
Living and well; awaiting another look	0	—
Living with residual	1	7
Dead of cancer	7	Average 15. Range 7-21
Dead (of cause other than cancer)	0	—
Operative deaths	3	—

* Four patients were free of cancer at the 3rd operation, and one patient was free of cancer at the 6th operation.
Status as of July 1, 1954.

in lymph node positive cases has been done in this clinic for gastric, colic and rectal cancer, it is in instances of colic cancer that the method appears to have particular value.[13] Time may prove, however, as we come to do the primary operation better in gastric cancer that the "second-look" procedure may have real merit there too. The accompanying table suggests that a definite salvage of life is resulting from the application of this principle of management to instances of lymph node positive cases of colic cancer. Inasmuch as only six years have now elapsed since the first cases in the series were done, a longer time will have to pass before it can be learned whether the "second-look" procedure will erase largely the present great disparity in accomplishment between the lymph node positive and negative cases of colic cancer.

The usual interval before reoperation has been approximately six months. "Second-look" procedures at intervals of six months are con-

tinued as long as residual cancer is found. In other words a final negative look is employed as the hallmark of a successful conversion. The accompanying table (I) indicates that five of sixteen patients who still had evidence of residual cancer at the first "second-look" procedure became cancer negative through the agency of reoperation. In one instance, six operations were necessary to effect the conversion.

Rectum

No effort will be made in this account to report upon the effectiveness of surgery in cancer of the rectum. If all adults submitted to an annual proctoscopic examination, the cure rate of rectal cancer would be improved considerably. Abdominoperineal excision of the rectum with performance of colostomy is the operation of choice for all lesions less than 10 cm. from the anus; it is also the best operation for all lesions with demonstrable local extensions into the adjacent pararectal tissues. For lesions confined to the bowel and 10 cm. or more from the anus, a satisfactory cancer operation can be done with restoration of intestinal continuity. The results of this somewhat more limited excision of pelvic tissue appear to compete quite favorably with the end results of the more formidable abdominoperineal procedure.

Cancer Detection Studies

Is it a reasonable assumption that if all visceral cancers could be diagnosed early that the majority would have no metastatic lymph node deposits? Surgical therapy is posited at least in part on this belief. Some studies of my associates, Drs. C. R. Hitchcock and J. B. Aust,[14] who direct the operation of our Cancer Detection Center would appear to lend tenable support to such a proposition. Of patients attending the Cancer Detection Center found to be achlorhydric and who on further study were found to have a gastric cancer, Hitchcock observed on reinterrogating them that nine out of fourteen patients found to have gastric cancer were completely asymptomatic. Of this group only three had positive lymph nodes; six of the nine patients are alive. The remaining five of the fourteen gastric cancer patients, on subsequent inquiry were found to have symptoms; four of these had positive lymph nodes; only one of the five is still alive.

The situation is even more striking in colic and rectal cancer. During the same interval of time (March 1, 1948 to Sept. 1, 1954) Hitch-

cock and his associates found a total of twenty-six patients with rectal (eight) or colic (eighteen) cancer. Of these twenty-six patients, eighteen were completely asymptomatic; four of the eighteen had microscopic cancer in the lymph nodes; seventeen are alive; the death in this group was owing to a cerebrovascular accident. The remaining eight patients on reinterrogation were found to have had some symptoms; three had metastatic cancer in the regional lymph nodes; only three patients are alive.

Summary

In conclusion, I would stress the importance of present efforts directed at cancer detection. While we await the arrival of biologic or organ scrutiny tests which will simplify the problem of earlier recognition, we must continue to seek out asymptomatic cancers, employing the techniques now in vogue in many Cancer Detection Centers. Aggressive surgery makes a good showing even in gastric cancer when the disease is local. For the two year period of 1948 through 1949, 90 per cent of the survivors of gastrectomy who were found to be lymph node negative for gastric cancer were alive five years later. As more aggressive operations are done, and more complete histological examinations are made upon the excised tissues, it appears that metastatic deposits in the regional lymph nodes are indeed frequent.

The five year survival of all cases of gastric cancer seen at the University Hospitals during the sixteen year period of this study (1936-1949 inclusive) has been 10.3 per cent. For the six year period from 1944 through 1949, this figure is 12.4 per cent. Prior to 1930, there was not a single instance of a five year survival following resection for a gastric cancer on the hospital records of the University of Minnesota surgical clinic. Since Jan. 1, 1936 there have been 109 patients who have survived for more than five years following resection. Of these three had lymphosarcoma; two had leiomyosarcoma, and 104 had gastric carcinoma.

If comparable improvement in the early recognition of gastric cancer can be made in the next fifteen years as has occurred in its surgical management, we shall be able to record presently important gains and notable betterment over the current accomplishment in the problem of gastric cancer. Surgery is making life worthwhile for many who suffer from cancer. When operations for early visceral cancer become the

rule, the present day accomplishment will seem poor indeed. Moreover, the operations of today for cancer of the stomach are incomplete in the light of the knowledge gained in "second-look" procedures undertaken in lymph node positive cases of gastric cancer. These studies indicate that the most frequent site of residual cancer following the current methods of aggressive surgery for gastric cancer is in the portal triad and the cystic duct area. These lymph nodes must be removed completely in the primary operation. Obviously, the incompleteness of the present day operation for gastric cancer is one of the factors responsible for the modest accomplishment.

The "second-look" procedure has been the means of ridding some lymph node positive patients with colic cancer of residual cancer encountered at the time of reoperation. Total or near total colectomy is a more complete operation for colic cancer and presently should come to replace the less aggressive segmental and hemicolectomy conventionally performed now for colic cancer.

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MODERN THERAPEUTIC MEASURES IN CANCER AND THEIR EFFECTIVENESS: RADIOLOGY*

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RADIATION therapy is used in cancer sometimes for essentially curative purposes and also, often, for palliative relief. The situations in which it is used are often unsuitable for management by any other method now available. When applied with wisdom, it combines a large amount of clinical experience and judgment with exacting scientific knowledge of physics and radiobiology and utilizes the most modern developments of engineering and nuclear and atomic research.

The role of the physician must always come first. No amount of applied science, no matter how critically exact, can replace or preempt the attention which must be given to the patient's general metabolic and psychological state, the use of adjuvant drugs, and the clinical eye kept trained on the occurrence of complications or new developments. When treating cancer, manifestations of metastasis often require major alterations in the plan of palliative therapy or shifting from curative to palliative objectives at any time. Simple palpation or observation is often as important as more advanced studies with blood chemistry determinations, x-ray examinations, etc. The physician must know the many and varied patterns of tumor spread through local extension, lymphatic spread, hematogenous spread, or through body cavities.

Perhaps the most dramatic recent development has been in the increase of the methods and sources for radiation therapy. Electronic and mechanical engineering and the by-products of atomic energy have swelled the list of available methods to something like this extent:

1. External Beam
   - A. Low-Intermediate-High Voltage
   - B. Super Voltage

* Presented at the Stated Meeting of The New York Academy of Medicine, November 4, 1954, as part of the Eighth A. Walter Suiter Lecture program. This meeting was arranged by the Committee on Public Health with the cooperation of the New York City Cancer Committee, as a Symposium on "Cancer — What We Know Today".

C. Gamma Beam
D. Electron Beam
E. Neutron Beam
F. Proton Beam
G. Cross-Fire: Rotation

2. Interstitial Sources
   A. Radium Needles–Radon
   B. Other Isotopes–Co^{60}
3. Interstitial Colloidal Isotopes
   Au^{198}; Chromic Phosphate (P^{32})
4. Intracavitary
   A. X-Ray
   B. Radium-Radon-Other Isotopes–Co^{60}
   C. Liquid Isotopes–Co^{60}
   D. Colloidal Isotopes–Au^{198}
5. Parenteral Isotopes
   A. P^{32}–Oral and I.V.
   B. I^{131}–Oral and I.V.
   C. Colloidal Au^{198}–I.V.
   D. Others–Na^{24}

Much interest has been attracted to the use of apparatus which generates x-ray beams at energies of one and two million volts up to twenty-two million volts, and higher–commonly called super voltage, but more properly called mega-voltage apparatus. Some of these beams are essentially duplicated in apparatus employing very large amounts of radioactive isotopes and shielded so that their gamma beams may be used at a considerable distance and in quality ranges comparable to 400 to 2,000 kilovolt x-ray therapy. While no truly new, or radically different effect is to be expected from this type of radiation, it is hoped that the ease of delivering larger doses to greater depths with less discomfort to the patient will justify their further development.

The use of electron, proton and neutron beams is still in the experimental stage. Mechanical devices for improving the delivery of radiation to deeper parts by cross-firing and rotation therapy techniques offer much promise.

In some instances, interstitial sources of radiation seem preferable because of the site and extent of the local tumor, and we have available greatly improved radium needles and radon seeds, as well as ingenious substitutes in Co^{60}, Au^{198} grains, radiotantulum wire, and other radioactive isotopes.

Interstitial radiation may also be delivered with colloidal radioactive isotopes of gold and phosphorus.

In the cavities of the body, the insertion of x-ray beams and, in special instances, of the x-ray tube target has been advantageously employed for special problems such as cancer of the cervix. Radium, radon, or other radioactive isotopes, such as Co^{60}, may also be used, and have a major field of application in cervical cancer, and intraoral cancer. It is now possible to use liquid radioisotopes for the radiation of cavities which may be filled, such as the bladder. Colloidal radioactive isotopes can be instilled into the peritoneal and pleural cavities, such as the use of Au^{198} for the control of malignant ascites and pleural effusions.

Radiation therapy of greater complexity, but of tantalizing promise, is found in the use of radioactive isotopes which depend on metabolic and physical localization when introduced parenterally. The most familiar applications of this principle are in the use of radioactive phosphorus, orally or intravenously, in the treatment of polycythemia vera and certain leukemias; and in the remarkable localization of radioactive iodine in certain metabolically active thyroid cancers.

Less spectacular, but of increasing importance with the use of these many methods, is close cooperation with the radiological physicist and the use of his contributions. Radiation dosage may now be computed to levels of accuracy far beyond that of our clinical judgment. It is quite important, however, for it avoids summating physical errors onto those due to the vagaries of malignant disease or to the limits of medical knowledge. For beam radiations, full expressions of air, skin, tissue dose can be derived either in selected planes, or in three dimensional contours. Dosage computations with radioactive isotopes are more difficult but are also probably of even greater importance because of the lesser experience with these agents. Radiological physics has also furnished us with a wealth of precision instruments for determining the distribution of radioactive materials, the control of beam producing apparatus, and the analysis of the health and safety aspects of radiation hazards affecting the patients, the investigators, and the innocent bystanders.

The newest field of investigation is in the actions of radiations on living tissues, both normal and malignant. Not only does this throw light on the efficacy of radiation therapy, but is also of importance in adding to our information concerning the characteristics of malignant disease itself. Some of the influences of cell metabolism and the inter-

actions of hormones and chemotherapeutic agents on radiation sensitivity hold promise for future development. Though still in its infancy, this field of investigation is showing great promise in the explorations of dosage fractionation and the relative biological efficiency of different forms of radiation.

Radiation therapy of cancer of the skin, lip, larynx, cervix and fundus has become well established as the definitive agent for curative management in a large proportion of cases. In many more, it is used as the primary method of choice in the hope that cure may be obtained, but with uncertainty as to whether palliation may be all that can be achieved. In frankly advanced malignancy, palliative radiation therapy often achieves amazingly long management of a variety of tumors. A fragmentary list of situations in which it may be of major importance is as follows:

1. Bone: Pain, fracture, disseminated disease.
2. Local: Pain, ulceration, tumefaction, delay of spread, bleeding, ascites, pleural effusion.
3. Lymph Nodes: Ulceration, tumefaction, delay of spread, bleeding.
4. Pulmonary Metastasis: Cough, bleeding, pain, venous obstruction.
5. Lymphomas and Leukemias: Fever, malaise, local tumefaction, splenic enlargement.
6. Indirect Hormonal Effect: Radiation to the ovaries.

Enthusiastic though we may be to obtain total and unequivocal cures for malignant disease, the prolongation of useful and enjoyable life is an equally noble aim for the physician.

We do not yet know how much more can be achieved with the further development of radiation therapy. There is little evidence that we can expect a great qualitative improvement in radiation effect, but much may be done in employing the most advantageous distribution of radiations, choosing the optimal radiation source for each problem, and employing the full cooperation of radiological physics and radiobiology. Combined with expert clinical judgment and humanitarianism, the physician can hope to make long strides in the best interests of the cancer patient. We need to use fully the agents and techniques which are already at hand. If we continue to develop and use new methods, we can expect still further improvement in the control of the growth of cancer and in the alleviation of suffering due to it.

CANCER CHEMOTHERAPY*

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THE inclusion of a discussion of tumor chemotherapy in a lecture on the practical clinical aspects of neoplastic disease is a recognition of the important problem presented by widespread cancer. At the present time we in the medical profession have a major responsibility to make the diagnosis of malignant disease ever earlier and then to transfer our patient to a qualified surgeon or radiotherapist for curative treatment. At this particular moment in human history, however, it must be realistically acknowledged that only about one third of all patients with malignant neoplastic disease are alive five years after the diagnosis has been established. It has been estimated that assiduous and skillful application of currently available diagnostic and therapeutic measures could double the salvage rate and certainly this is a most worth while goal toward which to drive. But now, and in the foreseeable future, we must also be concerned with the treatment of incurable cancer.

The introduction of a presentation of the current status of cancer chemotherapy must emphasize that there are no drugs now available which can cure any disseminated neoplastic disease. In spite of this fact, drugs are useful and indicated in the medical management of a number of human tumors. Figure 1 presents those diseases in which, at some stage in their natural history, chemotherapeutic agents should be considered.

A. *Carcinoma of the Prostate:* In patients who have demonstrably inoperable disease manifested by 1) an elevation of the serum acid phosphatase, 2) osseous metastases, usually osteoblastic, or 3) clinically evident soft tissue metastases, bilateral orchiectomy and the administration of 5-15 mgm. of stilbestrol daily or some other potent estrogen, is the

* Presented at the Stated Meeting of The New York Academy of Medicine, November 4, 1954, as part of the Eighth A. Walter Suiter Lecture program. This meeting was arranged by the Committee on Public Health with the cooperation of the New York City Cancer Committee, as a Symposium on "Cancer — What We Know Today".
Studies of clinical cancer chemotherapy conducted at the Francis Delafield Hospital are supported in part by a grant from the National Cancer Institute, United States Public Health Service.

DISEASE	Estrogen	Androgen	Cortisone	Nitrogen Mustard	TEM	Anti-Fol.	6MP	MYLERAN	ThioTEPA	Urethane
Ca PROSTATE	●									
Ca ♂ BREAST	●									
Ca ♀ BREAST	●	●								
Ca LUNG				●						
Ca OVARY				●	●				●	
LEUKEMIA: *Acute* *Chronic Lymphatic* *Chronic Myelocytic*			● ●	● ●	● ●	●	●	●		
HODGKINS			●	●	●				●	
LYMPHOSARCOMA: *Giant Follicular* *Lymphocytic* *Lymphoblastic*			●	● ●	● ●				●	
MULTIPLE MYELOMA			●							●

Figure 1

treatment of choice. The combination of castration and estrogen has been demonstrated to be the most effective therapeutic regimen in this disease, leading to significant prolongation of life.

B. *Carcinoma of the Male Breast:* This is a relatively rare tumor and usually is recognized only after it has become incurable by surgery or radiotherapy. Like carcinoma of the prostate, the malignant cancer cells arising in the male breast are androgen dependent and castration followed later by estrogen is indicated if the disease is widespread. Remissions even more favorable than those noted in prostatic cancer can be anticipated after this regimen has been initiated.

C. *Carcinoma of the Female Breast:* In this country, breast cancer in women is the most frequent of all malignant tumors with the exception of skin epitheliomas. When the physician has determined that the tumor is inoperable due to distant spread or too extensive regional involvement, or when the disease is found to be metastatic after radical mastectomy, several therapeutic avenues are available. In premenopausal patients, castration is indicated. Radiotherapy is effective for the control of regional disease and is preferable to hormones in the treatment of disseminated disease which is only producing symptoms in a few well localized areas. When disease is both widespread and diffusely symptomatic, hormone therapy should be considered. In all age groups testosterone propionate in dosage of 300-600 mgm. weekly may be given. Eighty per cent of patients will receive symptomatic benefit from androgen therapy although only a small fraction will have significant objective regression of tumor. When subjective benefit has been obtained, the male sex hormone therapy can be more conveniently con-

tinued by methyl testosterone given sublingually. This route of administration seems to avoid the hepatotoxic reaction of the drug which occurs occasionally when it is absorbed directly into the portal circulation. Virilization, salt and water retention and, rarely, tumor stimulation are general reactions which may accompany androgen therapy.

In women well past the menopause, estrogens (usually stilbestrol) may be substituted for androgen. Again, subjective improvement is more frequently noted than is objective tumor regression. Edema, uterine bleeding and acceleration of tumor growth must be watched for on this regimen.

D. *Cancer of the Lung:* Bronchogenic carcinoma is better prevented than treated in this day and age! Surgery and radiotherapy cure relatively few men (or women) with this cancer because, so frequently, it has permeated mediastinal structures when recognized or has metastasized distantly. Unhappily, available chemotherapeutic agents offer little. When tumor infiltration of the mediastinum leads to pressure on the great vessels interfering with the venous return to the heart and producing the signs and symptoms of the superior mediastinal compression syndrome, intravenous nitrogen mustard may provide transient improvement. This is shortlived unless radiotherapy, initiated at the same time, more effectively curbs tumor growth. The toxicity of nitrogen mustard is manifested by immediate nausea and vomiting and by depression of bone marrow function.

E. *Carcinoma of the Ovary:* Chemotherapy is only indicated when surgery or radiotherapy is no longer advisable because of extent of disease. This usually means a patient with marked ascites, extensive, palpable tumor masses, and evidences of cachexia. In this difficult therapeutic problem nitrogen mustard or preferably its near relative triethylene melamine will produce objective tumor regression and subjective benefit in about 25 per cent of the patients. Triethylene melamine or TEM is given by mouth in doses of 5 mgm. daily for three to four days. It produces very much less nausea and vomiting than HN_2 but does reversibly depress bone marrow function. The remissions achieved in those who do respond vary between six and eighteen months.

F. *Leukemia:* Since the clinical features of the acute and chronic forms of this blood dyscrasia differ so tremendously, it is not surprising that the treatment must be varied depending upon the diagnosis.

In acute leukemia, radiotherapy has practically no place. Only

chemotherapeutic agents are indicated and these still leave much to be desired. Three agents are available: Cortisone, the folic acid antagonists such as amethopterin and aminopterin, and 6-mercaptopurine or as it is known commercially, Purinethol. These drugs have all been developed as anti-leukemic agents since 1947 and it can be confidently anticipated that new and more effective compounds will be made available from active research work now in progress. This is an important consideration in the decision to treat the disease now since prolongation of life is measured in months rather than years.

Each one of the drugs can induce clinical and hematological remissions. In acute leukemia of children cortisone rapidly improves 60 to 70 per cent of the patients treated. Because high dosage (100-200 mgm. daily) is required, the clinical manifestations of hypercorticism usually appear early. This is not too great a price to pay for the fall of a hectic temperature to normal, cessation of purpura, decrease in visceral infiltrations and return of appetite and sense of well-being. Inevitably, however, exacerbations of the disease occur which respond progressively less well or not at all to the cortical steroid. In 50 to 60 per cent of children with acute leukemia amethopterin given in oral doses of 2.5-5.0 mgm. daily causes remissions. The appearance of ulcers of the buccal mucous membrane or pancytopenia is evidence of toxicity of the drug which must be looked for. As with cortisone, dramatic remissions of disease can be achieved with this folinic acid antagonist which miraculously may transform a moribund youngster to apparent normal in a few weeks. Distressingly, also like cortisone, the disease relatively quickly becomes refractory to the compound and further administration is ineffective. The most recent agent introduced is Purinethol or mercaptopurine. In 30 to 40 per cent of the instances of childhood leukemia remissions are achieved when doses of 2-3 mgm. per kilogram of body weight are given by mouth each day. With time, in those patients who initially benefited, drug-resistant leukemic cells develop which make further treatment useless and hazardous.

When the three drugs just mentioned are used serially together with appropriate supportive measures such as transfusions and antibiotics, 50 per cent of children with acute leukemia will be alive at least one year after the diagnosis has been made. This fact is to be contrasted with the 5 per cent one year survival of leukemic children prior to 1947.

The biology of acute leukemia in adults differs from that of children possibly because the disease is predominantly myeloblastic in the older age group and lymphoblastic in children. In any event the acute blood dyscrasia in adults responds far less regularly to the anti-leukemic drugs, only about 15 per cent showing hematological and clinical improvement. Because bleeding manifestations are common together with constitutional reactions, the drug which offers the most in adult acute leukemia is cortisone. Although only rarely does the hormone produce significant change in the peripheral blood picture, it does induce symptomatic improvement frequently.

The chronic leukemias present a far more favorable problem therapeutically. One of the primary questions after the diagnosis has been made is the optimal time to initiate therapy. The consensus of hematologists at the present is to withhold treatment until symptoms appear. In other words treat the patient rather than his blood count. Conventional treatment of the chronic blood dyscrasias is by radiotherapy. Alternative and equally effective regimens using drugs are now available. In chronic lymphatic leukemia the nitrogen mustard compounds are effective and TEM is the agent of choice. Using small daily doses, a titration can be carried out with the hemogram and the clinical status of the patient providing helpful end points.

In chronic myelocytic leukemia, another drug, in addition to the mustard group, is available. This is Myleran which is only of value in this disease. Its administration may be followed (and usually is) by a reduction of the peripheral blood count to normal levels with an appropriate modification of blood cell morphology, and a decrease to disappearance of the visceral infiltrations. Daily oral doses of 10 mgm. are followed by smaller maintenance dosage when remission has been achieved. Myleran, like most of the other drugs discussed, can depress hematopoiesis.

There are certain generalizations to be made in the treatment of the malignant lymphomas which include Hodgkin's disease and the lymphosarcomas. Unlike the leukemias there is evidence to indicate that the lymphomas may arise in a single focus and then metastasize rapidly. As with epithelial tumors this carries the implication that early diagnosis and aggressive therapy to localized disease may be curative. Bear this in mind when unexplained persistent and asymptomatic lymphadenopathy is noted either by your patient or by you in the

course of physical examination. Clinically localized malignant lymphomas should be treated by cancericidal doses of x-ray. Chemotherapy has no place in the treatment of localized disease since currently available drugs have not cured a single patient with these diseases. When the lymphomas are evidently disseminated and symptomatic, chemotherapy may be reasonably considered.

G. *Hodgkin's Disease:* Nitrogen mustard by intravenous administration may be given to patients with marked constitutional reaction such as high fever, asthenia, pruritus and profound anorexia. In 80 per cent of patients rapid subjective and objective improvement will occur. In individuals who are less acutely ill, TEM given on an ambulatory basis is frequently helpful. A more recently introduced relative of nitrogen mustard is thioTEPA or more formally, thiotriethylene phosphoramide. This compound is given intravenously in doses of 5-10 mgm. daily until the total amount has reached 50-70 mgm. No nausea or vomiting is produced, but depression of bone marrow function does occur. The exact place in the treatment of Hodgkin's disease has not yet been assigned to this compound.

H. *Lymphosarcoma:* The histological classification of the lymphosarcomas has some clinical importance. The giant follicular type is relatively benign and responds well and for long time intervals to radiotherapy or chemotherapy. The small cell or lymphocytic form of lymphosarcoma is more malignant than the giant follicular lymphosarcoma and less so than the large cell or lymphoblastic lymphosarcoma. This latter disease does not respond well to chemotherapy or radiotherapy when it is widespread and is associated with constitutional signs and symptoms. Recent incomplete observations suggest that thioTEPA may be particularly useful in therapy.

I. *Multiple Myeloma:* An understanding of the natural history of this disease is a prerequisite to its medical management. Multiple systems may be directly or indirectly involved by the tumor. Neurological complications may arise due to compression of the spinal cord by extradural neoplasm or peripheral neuropathy secondary to para amyloid deposition in and about nerve sheaths. Hypercalcemia can occur as a result of extensive skeletal destruction with changes in renal and cardiac function. Renal function can also be impaired by deposition of Bence-Jones protein in the tubules. The replacement of the bone marrow by the malignant plasma cells can lead to pancytopenia or depression of

any one of the formed elements, and skeletal pain, the symptom which is most distressing to the patient.

The treatment of multiple myeloma depends upon the use of radiotherapy, chemotherapy and non-specific measures such as hydration and blood transfusions. Radiotherapy is valuable for the control of pain localized in a few areas. When the symptomatology is diffuse chemotherapy with urethane and cortisone is the best available regimen. The urethane is given in daily oral doses of 2.4-3 grams together with 100 mgm. of cortisone in divided amounts. Weekly examinations of the blood count are necessary in order to avoid hazardous depression of bone marrow function by the urethane.

This completes a thumbnail sketch of clinical cancer chemotherapy. It is to be emphasized that the proper care of patients with widespread cancer must include attention to medical problems which may arise as complications of the tumor or unrelated to it. The application of general supportive measures, anti-tumor chemotherapy, palliative radiotherapy and surgery can be expected to provide an extension of the period of useful and comfortable living to patients with disseminated disease.

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

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November 4, 1955

TOXIC EFFECTS OF THERAPEUTIC AGENTS

Moderator: PAUL REZNIKOFF

ERRATUM

In the September 1955 number of the Bulletin, on page 648, line 2, of the Transcript of a Panel Meeting on CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS, there is a typographical error in dosage of the intramuscular use of Terramycin. This should be corrected to read: ". . . the intramuscular preparation of Terramycin using 100 mg. every 12 hours . . ." We regret this error.—Ed.